表 2-18 統合コホートにおける平均、標準偏差、最小値、最大値(Hba1c)

(Hb1ac)

	コホートID	対象者数	平均	標準偏差	最小	最大	欠測
男性	1	908					
	2	6,919					
	3	1,269	5.7	1.3	4.5	9.4	1,256
	4	1,624					
	5	4,398					
	6	1,939					
	9	1,521					
	10	1,162	5.6	0.8	3.9	11.1	1
	11	11,600					
	12	4,244					
	13	3,442	5	0.8	3.2	11.8	276
	計	39,026	5.2	0.8	3.2	11.8	34,686
女性	1	1,081					
	2	9,345					
	3	1,905	5	0.3	4.5	5.5	1,896
	4	3,573					
	5	2,659					
	6	2,596					
	9	3,149					
	10	1,574	5.5	0.8	4	12	1
	11	20,102					
	12	5,394					
	13	4,760	4.9	0.7	3.1	13.5	370
	計	56,138	5.1	0.8	3.1	13.5	50,166

表 2-19 統合コホートにおける平均、標準偏差、最小値、最大値(アルブミン)

(アルブミン)

	コホートID	対象者数	平均	標準偏差	最小	最大	欠測
男性	1	908					
	2	6,919					
	3	1,269					
	4	1,624					
	5	4,398	4.6	0.2	3.7	5.5	1,696
	6	1,939					
	9	1,521	4.5	0.3	2.8	5.4	17
	10	1,162	4.3	0.3	3.1	5	0
	11	11,600					
	12	4,244	4.4	0.3	3	5.4	65
	13	3,442	4.5	0.3	2.9	5.6	275
	計	39,026	4.5	0.3	2.8	5.6	26,312
女性	1	1,081					
	2	9,345					
	3	1,905					
	4	3,573					
	5	2,659	4.4	0.2	3.7	5.1	1,210
	6	2,596					
	9	3,149	4.5	0.3	2.5	5.5	44
	10	1,574	4.2	0.2	2.6	5	1
	11	20,102					
	12	5,394	4.4	0.2	1.5	6	79
	13	4,760	4.4	0.3	3.1	5.4	370
	計	56,138	4.4	0.3	1.5	6	40,306

表 2-20 統合コホートにおける平均、標準偏差、最小値、最大値(飲酒・合)

(飲酒・合)

	コホートID	対象者数	平均	標準偏差	最小	最大	欠測
男性	1	908					
	2	6,919	1.4	1.0	0.0	5.0	344
	3	1,269					
	4	1,624					
	5	4,398					
	6	1,939	1.0	0.8	0.0	3.0	12
	9	1,521					
	10	1,162					
	11	11,600	1.8	1.0	0.1	20.0	4,270
	12	4,244					
	13	3,442					
	計	39,026	1.5	1.0	0.0	20.0	23,194
女性	1	1,081					
	2	9,345	0.2	0.5	0.0	5.0	1,866
	3	1,905					
	4	3,573					
	5	2,659					
	6	2,596	0.1	0.3	0.0	3.0	27
	9	3,149					
	10	1,574					
	11	20,102	0.9	0.7	0.1	10.0	17,504
	12	5,394					
	13	4,760					
	計	56,138	0.3	0.6	0.0	10.0	43,492

表 2-21　統合コホートにおける頻度(総死亡)

(総死亡)

	コホートID	対象者数	総死亡	%
男性	1	908	133	14.6
	2	6,919	548	7.9
	3	1,269	282	22.2
	4	1,624	287	17.7
	5	4,398	85	1.9
	6	1,939	150	7.7
	9	1,521	708	46.5
	10	1,162	189	16.3
	11	11,600	1,444	12.4
	12	4,244	1,091	25.7
	13	3,442	448	13.0
	計	39,026	5,365	13.7
女性	1	1,081	86	8.0
	2	9,345	302	3.2
	3	1,905	225	11.8
	4	3,573	290	8.1
	5	2,659	20	0.8
	6	2,596	65	2.5
	9	3,149	1,182	37.5
	10	1,574	155	9.8
	11	20,102	1,038	5.2
	12	5,394	919	17.0
	13	4,760	362	7.6
	計	56,138	4,644	8.3

表 2-22　統合コホートにおける平均、標準偏差、最小値、最大値(観察人年)

(観察人年)

	コホートID	対象者数	平均	標準偏差	最小	最大	欠測
男性	1	908	18	4.4	0.6	22.1	0
	2	6,919	6	1.4	0	6.7	0
	3	1,269	9.6	2.8	0.2	11.7	0
	4	1,624	9.6	2.1	0	10.6	0
	5	4,398	10.5	3.1	0	12.2	0
	6	1,939	9.2	2.9	0.1	11	0
	9	1,521	13.5	5.2	0.5	19.5	0
	10	1,162	9.9	3.7	0	12	0
	11	11,600	9.4	2.2	0.1	11.6	0
	12	4,244	16.8	4.5	0	19	0
	13	3,442	9.4	1.8	0.1	10	0
	計	39,026	10.1	4.3	0	22.1	0
女性	1	1,081	18.5	4.0	0.7	22.2	0
	2	9,345	6	1.5	0	6.7	0
	3	1,905	10.3	2.6	0.1	11.7	0
	4	3,573	10.1	1.4	0	10.6	0
	5	2,659	10.5	3.2	0	12.5	0
	6	2,596	9.2	2.9	0.1	11	0
	9	3,149	14.5	4.6	0.5	19.5	0
	10	1,574	10.6	3.2	0	12	0
	11	20,102	9.7	1.9	0	11.6	0
	12	5,394	17.5	3.8	0.1	19	0
	13	4,760	9.6	1.4	0.1	10	0
	計	56,138	10.3	4.1	0	22.2	0

表 2-23　統合コホートにおける頻度(喫煙)

(喫煙)

	コホートID	対象者数	なし	止めた	あり	不明
男性	1	908	229	0	523	156
			25.2	0.0	57.6	17.2
	2	6,919	1,413	1,997	3,188	321
			20.4	28.9	46.1	4.6
	3	1,269	649	0	620	0
			51.1	0.0	48.9	0.0
	4	1,624	725	0	899	0
			44.6	0.0	55.4	0.0
	5	4,398	1,178	591	2,629	0
			26.8	13.4	59.8	0.0
	6	1,939	544	229	1,164	2
			28.1	11.8	60.0	0.1
	9	1,521	191	417	723	190
			12.6	27.4	47.5	12.5
	10	1,162	233	353	576	0
			20.1	30.4	49.6	0.0
	11	11,600	2,491	2,728	5,948	433
			21.5	23.5	51.3	3.7
	12	4,244	777	794	2,666	7
			18.3	18.7	62.8	0.2
	13	3,442	722	811	1,864	45
			21.0	23.6	54.2	1.3
	計	39,026				
女性	1	1081	804	0	65	212
			74.4	0.0	6.0	19.6
	2	9345	6,736	121	355	2,133
			72.1	1.3	3.8	22.8
	3	1905	1,859	0	46	0
			97.6	0.0	2.4	0.0
	4	3573	3,471	0	102	0
			97.1	0.0	2.9	0.0
	5	2659	2,585	27	47	0
			97.2	1.0	1.8	0.0
	6	2596	2,467	14	87	28
			95.0	0.5	3.4	1.1
	9	3149	2,618	96	297	138
			83.1	3.0	9.4	4.4
	10	1574	1,432	33	109	0
			91.0	2.1	6.9	0.0
	11	20102	17,792	226	705	1,379
			88.5	1.1	3.5	6.9
	12	5394	4,793	119	476	6
			88.9	2.2	8.8	0.1
	13	4760	4,139	123	433	65
			87.0	2.6	9.1	1.4
	計	56,138				

各コホートの結果で、上段は頻度、下段は各コホート内での割合(%)を示す。

コホート ID：1, 3, 4:「やめた」と「なし」の分類がないため「なし」に分類した。

表 2-24　統合コホートにおける頻度(喫煙本数)

(喫煙本数)

	コホートID	対象者数	なし	止めた	1-20本	21本以上	不明
男性	1	908	229	0	329	194	156
			25.2	0.0	36.2	21.4	17.2
	2	6,919	1,413	1,997	2,241	706	562
			20.4	28.9	32.4	10.2	8.1
	3	1,269	599	49	374	237	10
			47.2	3.9	29.5	18.7	0.8
	4	1,624	725	0	729	159	11
			44.6	0.0	44.9	9.8	0.7
	5	4,398	1,178	591	1,710	894	25
			26.8	13.4	38.9	20.3	0.6
	6	1,939	544	229	342	822	2
			28.1	11.8	17.6	42.4	0.1
	9	1,521					
	10	1,162	233	353	309	267	0
			20.1	30.4	26.6	23.0	0.0
	11	11,600	2,491	2,728	4,405	1,543	433
			21.5	23.5	38.0	13.3	3.7
	12	4,244	777	794	1,635	1,031	7
			18.3	18.7	38.5	24.3	0.2
	13	3,442	722	811	1,239	625	45
			21.0	23.6	36.0	18.2	1.3
	計	39,026					
女性	1	1081	804	0	60	5	212
			74.4	0.0	5.6	0.5	19.6
	2	9345	6,736	121	272	23	2,193
			72.1	1.3	2.9	0.2	23.5
	3	1905	1,851	8	41	4	1
			97.2	0.4	2.2	0.2	0.1
	4	3573	3,471	0	88	4	10
			97.1	0.0	2.5	0.1	0.3
	5	2659	2,585	27	41	0	6
			97.2	1.0	1.5	0.0	0.2
	6	2596	2,467	14	64	23	28
			95.0	0.5	2.5	0.9	1.1
	9	3149					
	10	1574	1,432	33	95	14	0
			91.0	2.1	6.0	0.9	0.0
	11	20102	17,792	226	666	39	1,379
			88.5	1.1	3.3	0.2	6.9
	12	5394	4,793	119	437	39	6
			88.9	2.2	8.1	0.7	0.1
	13	4760	4,139	123	395	38	65
			87.0	2.6	8.3	0.8	1.4
	計	56,138					

各コホートの結果で、上段は頻度、下段は各コホート内での割合(%)を示す。

表 2-25　統合コホートにおける頻度(飲酒)

(飲酒)

	コホートID	対象者数	なし	止めた	あり	不明
男性	1	908	214	0	535	159
			23.6	0.0	58.9	17.5
	2	6,919	1,049	556	5,114	200
			15.2	8.0	73.9	2.9
	3	1,269	507	0	762	0
			40.0	0.0	60.0	0.0
	4	1,624	412	459	753	0
			25.4	28.3	46.4	0.0
	5	4,398	812	50	3,536	0
			18.5	1.1	80.4	0.0
	6	1,939	398	0	1,529	12
			20.5	0.0	78.9	0.6
	9	1,521	204	86	963	268
			13.4	5.7	63.3	17.6
	10	1,162	379	88	694	1
			32.6	7.6	59.7	0.1
	11	11,600	2,173	581	8,510	336
			18.7	5.0	73.4	2.9
	12	4,244	849	247	3,142	6
			20.0	5.8	74.0	0.1
	13	3,442	1,197	231	1,969	45
			34.8	6.7	57.2	1.3
	計	39,026				
女性	1	1081	792	0	76	213
			73.3	0.0	7.0	19.7
	2	9345	5,636	228	1,656	1,825
			60.3	2.4	17.7	19.5
	3	1905	1,773	0	132	0
			93.1	0.0	6.9	0.0
	4	3573	3,039	494	40	0
			85.1	13.8	1.1	0.0
	5	2659	1,885	24	750	0
			70.9	0.9	28.2	0.0
	6	2596	2,049	0	520	27
			78.9	0.0	20.0	1.0
	9	3149	1,607	47	953	542
			51.0	1.5	30.3	17.2
	10	1574	1,414	17	141	2
			89.8	1.1	9.0	0.1
	11	20102	15,216	238	3,741	907
			75.7	1.2	18.6	4.5
	12	5394	4,236	83	1,065	10
			78.5	1.5	19.7	0.2
	13	4760	4,346	48	301	65
			91.3	1.0	6.3	1.4
	計	56,138				

各コホートの結果で、上段は頻度、下段は各コホート内での割合(%)を示す。

表 2-26　統合コホートにおける頻度(飲酒頻度)

(飲酒頻度)

	コホートID	対象者数	なし	時々	毎日	不明
男性	1	908				
	2	6,919	1,038	2,367	3,167	347
			15.0	34.2	45.8	5.0
	3	1,269				
	4	1,624				
	5	4,398	862	1,187	99	2,250
			19.6	27.0	2.3	51.2
	6	1,939				
	9	1,521				
	10	1,162				
	11	11,600				
	12	4,244	849	2,017	1,125	253
			20.0	47.5	26.5	6.0
	13	3,442				
	計	39,026				
女性	1	1081				
	2	9345	5,621	1,606	272	1,846
			60.1	17.2	2.9	19.8
	3	1905				
	4	3573				
	5	2659	1,910	625	0	124
			71.8	23.5	0.0	4.7
	6	2596				
	9	3149				
	10	1574				
	11	20102				
	12	5394	4,236	153	912	93
			78.5	2.8	16.9	1.7
	13	4760				
	計	56,138				

各コホートの結果で、上段は頻度、下段は各コホート内での割合(%)を示す。

2-2. 統合データベースを使用した解析

統合データベースの有用性と利用可能性を検討する目的で、共通項目の一部(主に検診検査項目)について、エントリ時年齢・コホートのみを調整したハザード比をコックス比例ハザードモデルにより推定した。エントリ時年齢は連続量、コホート効果はダミー変数としてモデルに取り込み男女別に推定した各項目のハザード比と 95%信頼区間を表 2-27 に示す。なお、下記の結果は各項目の検討に必要な他要因の交絡の影響を調整しておらず、要因の 2 次の効果などを統計モデルで考慮していないので、結果の解釈に注意が必要である。

表 2-27　エントリ時年齢・コホートのみを調整したときの各項目のハザード比

		男性			女性		
		ハザード比	95%CI		ハザード比	95%CI	
収縮期血圧	10mmHg	1.06	1.05	1.08	1.06	1.04	1.07
拡張期血圧	10mmHg	1.07	1.05	1.10	1.09	1.06	1.12
総コレステロール	10mg/dl	0.96	0.96	0.97	0.97	0.96	0.98
HDLコレステロール	10mg/dl	0.98	0.95	1.01	0.98	0.94	1.02
中性脂肪	10mg/dl	1.00	1.00	1.00	1.00	0.99	1.01
血糖	10mg/dl	1.03	1.02	1.04	1.04	1.03	1.05
尿酸		1.01	0.99	1.04	1.09	1.06	1.12
got		1.01	1.01	1.01	1.01	1.01	1.01
gpt		1.00	1.00	1.00	1.01	1.01	1.01
ggpt		1.00	1.00	1.00	1.00	1.00	1.00
クレアチニン		1.18	1.09	1.28	1.23	1.16	1.30
ヘモグロビン		0.96	0.94	0.97	0.96	0.95	0.98
BMI		0.96	0.95	0.97	0.99	0.99	1.00
喫煙	すわない	1.00	-	-	1.00	-	-
	止めた	1.15	1.05	1.25	1.24	1.04	1.49
	すう	1.55	1.44	1.67	1.40	1.26	1.56
	すわない	1.00	-	-	1.00	-	-
	やめた	1.17	1.06	1.28	1.34	1.07	1.69
	1-20本	1.55	1.43	1.68	1.51	1.32	1.72
	21本以上	1.48	1.33	1.65	1.83	1.19	2.82

次に収縮期血圧・年齢を階級別に分割したもとでのハザード比の算出を試みた。収縮期血圧を 10mmHG、エントリ時年齢を 10 歳刻みとし比例ハザードモデルの説明変数に取り込み推定されたハザード比をもとに、収縮期血圧 110mmHG 未満、年齢 40 歳未満のハザード比を 1 としたときのハザード比を図 2-1 に示す。なおハザード比の推定にあたり各コホートの効果など他要因の効果は調整されていないので考慮が必要である。

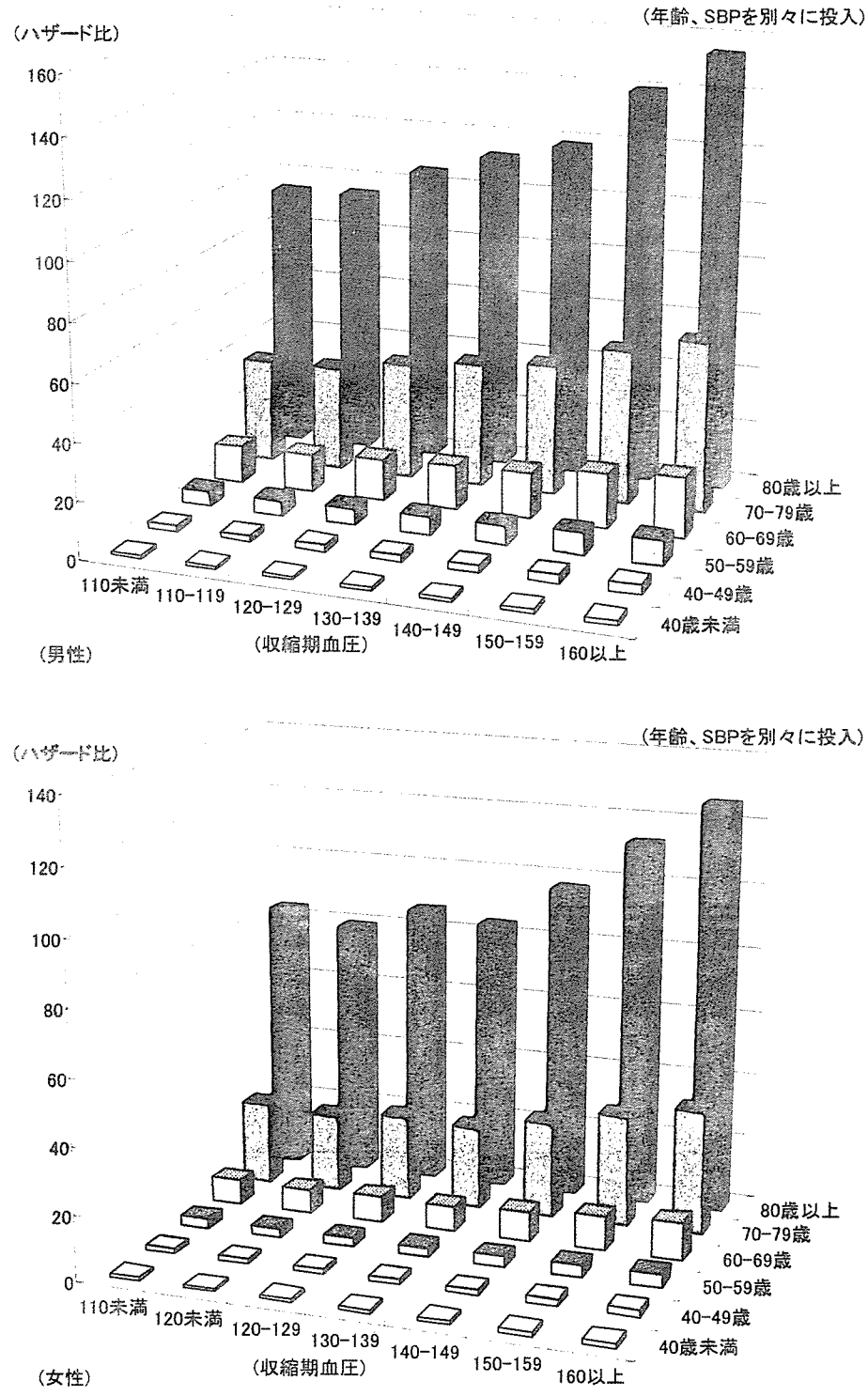

図 2-1　年齢階級別にみた総死亡と収縮期血圧との関連(上段:男性、下段:女性)
収縮期血圧 110mmHG 未満、年齢 40 歳未満のハザード比を 1 としたときのハザード比を示した。

3. 考察

本年度はこれからの解析の基礎となる統合データベースの作成を中心に作業をすすめるとともに、今後既存コホートを統合したデータベースを作成する際参考となるよう、統合データベース作成の過程を簡潔かつ明瞭にまとめた。本報告で示した統合データベース作成の過程はコホートデータの追加、共通項目の追加・変更などに柔軟に対応できる利点をもつ。本研究班においても次年度にはコホートの追加、さらには生活習慣関連項目をはじめとした共通項目の拡充の可能性があることから、今年度実施した作成過程の検討は今後とも有効であると考えられる。

次年度に追加が予定される共通項目として死因別死亡と疾患発症データの整理、それとともなう疾患発症に対応した個別の人年算出が必要となる。本統合データベースの最大の特性である膨大な対象者数から出生年ごとにみた検討(世代に関する解析)が可能となることから、世代の違いによる生活習慣要因の死亡・発生への影響検討が期待される。そのためにも観察開始日とその時点での年齢から生年の算出をする必要があろう。その他、心電図に関する項目の整理さらには食事をはじめとした生活習慣関連項目の整理が次年度の課題として挙げられる。

本報告では統合データベースを使用し、性・コホート別の基本集計、年齢・コホートのみを調整した検診項目のハザード比の算出を行うとともに、年齢階級別にみた総死亡と収縮期血圧との関連を視覚的に表現することを試みた。性・コホート別の基本集計は統合データベースを解析する第一段階の作業であり、統合コホートの拡充とともに繰り返し実施されるものと考えられる。また基本集計結果をチェックすることにより各コホートの特性を吟味し、統合データベース全体の特徴を把握することが可能となる。

共通項目(主に検診項目)に関し統計モデルを用いたハザード比を算出・検討することは、検診項目の評価を一つの目的とする本研究班に求められている重要な作業である。本年度はエントリ時の年齢とコホートのみを調整した結果であり、各項目の総死亡との関係についても単調増加／減少を仮定したにすぎず、BMI をはじめとする検査値の両極で高リスクをとる項目では適切でないおそれがある。またエントリ時の年齢を長期観察期間のデータで使用することは、年齢の影響調整の観点からも検討が必要な課題といえよう。

年齢階級別にみた総死亡と収縮期血圧との関連など視覚的な表現が必要な主題については、詳細かつ簡明な記述が求められる。通常のコホートの対象者数では収縮期血圧を 10mmHG、年齢を 10 歳刻みとし男女別にこれら関連を検討するのはサンプルサイズの問題から限界がある。これは約 10 万人(約 100 万人年)を誇る本研究班の統合データベースでしか実現できない主題であり、公衆衛生・予防医学の範疇を超え、診療ガイドラインへの活用という面で臨床医学に、科学的根拠に基づいたわが国の疾病構造を示すデータ(エビデンス)という面で保健医療行政に貢献すること多大と考えられる。

その実施にあたっては、コホート間の相違を考慮する必要があるか、他の調整要因を考慮すべきか、死亡率・罹患率で表現した方がハザード比よりもいいのではないか、など方法論上の課題も多くそれらへの対応が必要であるが、それとともに統合データベースは、結果への期待とその有用性に重きをおいた結果提示をすすめる必要があると考える。

4. 結論

本年度は本班分担研究者から提供されたデータをもとに統合データベースを作成し、その作業過程をまとめた。統合データベースの各項目に関し男女・コホート別集計を行い統合データの特性を記述した。単純な統計モデルによる各項目のリスク推定、収縮期血圧・年齢をカテゴリに分割したもとでのハザード比の算出を試み、統合データの有用性・可能性を示した。

Ⅱ．分担研究報告

2. JACC Study

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A. 研究の目的

日本人の生活習慣（例えば、喫煙習慣、食習慣、運動習慣など）は最近大きく変化している。それに伴い、がんによる死亡数、死亡率は、ともに年々増加しており、がんの有効な治療法を研究するだけでなく、日本人における適切ながん予防法を確立することが必要である。

1980年代後半、当時の青木國雄教授（名古屋大学医学部予防医学）を中心に疫学研究者が集まり、日本人におけるがん発生関連要因を大規模なコホート研究により検討することを目的にJACC Studyは開始された。このコホート研究は、約12万人の一般住民を追跡することにより、最近の日本人の生活習慣ががんとどのように関連しているかを明らかにすることを目的としている。その際、循環器疾患の疫学研究者もコホート研究に参画し、循環器疾患をエンドポイントとした追跡研究も行っている。

B. 研究対象と方法

ベースライン調査は全国45地区に住む住民を対象に、1988年から90年の間に自記式問診票で生活習慣、既往歴などの調査を行い、調査時に40～79歳だった110,792名（男46,465名、女64,327名）を追跡対象とした。45地区のうち、22地区では地区内に居住する該当年齢の全ての住民を対象とし、20地区では老人保健法に基づく基本健康診査を受診した住民を対象とした。2地区では、基本健康診査の受診者に加えてボランティアの参加者をも対象とし、残り1地区は被爆者検診受診者を対象とした。ベースライン時に対象者中約3.9万人については血清を採取し、1人チューブ5本（1本あたり約300μl）に分注し、-80℃で保管した。全ての情報は、各施設でコンピュータに電子情報として入力され、氏名や住所を除き個別のIDを付与した電子情報が事務局（名古屋大学医学部予防医学）に送付された。当時はまだ観察型の疫学研究参加に際して説明・同意手順を経ることは稀であったが、原則として、調査票の表紙に「調査への協力のお願い」として研究の説明をし、対象者に署名を依頼した。ただし、一部の地区では、地域の代表者への説明と了解の返事をもって、研究を実施した。

対照地域のうち31地区では、ベースライン調査から約5年後に中間調査を実施し、ベースライン調査対象者のうち約5万人の方から回答を得た。中間調査では、既往歴、食習慣や喫煙習慣について、特に5年間の変化に注目して調査を行った。

死亡情報は、1-2 年ごとに総務省に人口動態統計資料の目的外利用申請を行い、死亡小票をベースに 死亡年月日、死因を把握している。対象地区からの転出は各施設で市町村と協力して調査を進めている。24地区(対象数63,357名)では、地域のがん登録や主要病院への照会などにより、がんの罹患情報（部位、組織型、罹患年月日、手術の有無など）も把握する。

全ての情報は氏名や住所など個人を容易に特定できる情報を外し、個別 ID を付与して事務局に送付される。このコホート研究全体については、名古屋大学医学部倫理審査委員会で、循環器疾患の分析に関しては、筑波大学医の倫理特別委員会で倫理審査を受け、それぞれ承認を得た。

C. 研究成果

(1) 肥満度と循環器疾患死亡との関連

目的：日本人における肥満度と循環器疾患死亡との関連を明らかにする。

方法：文部科学省大規模コホート研究において、40～79 歳の 104,928 人（男性：43,889 人、女性：61,039 人、循環器疾患、がんの既往者除く）を対象として、1988-90 年から 1999 年末まで 1,042,835 人年を追跡した。肥満度は body mass index(BMI、kg/m^2)を用い、死因は ICD10 に従って分類した。BMI (kg/m^2＝23.0～24.9)を基準として、年齢、喫煙状況、飲酒量、高血圧の既往、糖尿病の既往、歩行時間、睡眠時間、教育歴と魚摂取頻度を調整した相対危険度(95%CI)を男女別に算出した。

結果：9.9 年間の追跡期間中、全脳卒中の死亡は男性 765 人、女性 685 人、脳内出血はそれぞれ 191 人、145 人、虚血性心疾患はそれぞれ 379 人、256 人、全循環器疾患はそれぞれ 1707 人、1432 人であった。BMI が 23.0～24.9 の群に対して、BMI 高値群(≧27.0)において虚血性心疾患死亡リスクが男女とも高く、その相対危険度は男性で 2.1(1.4-3.1)、女性で 1.6(1.0-2.6)であった。一方 BMI 低値群(<18.5)においては脳卒中、中でも脳内出血の死亡リスクが男女とも高く、その相対危険度は男性で 2.0(1.2-3.3)、女性で 2.3(1.4-4.0)であった。

結論：日本人において BMI の高値が虚血性心疾患のリスクを上昇させ、BMI の低値が脳内出血死亡リスクの上昇に関連することが示された。

Stroke

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Body Mass Index and Mortality From Cardiovascular Disease Among Japanese Men and Women: The JACC Study

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Body Mass Index and Mortality From Cardiovascular Disease Among Japanese Men and Women

The JACC Study

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Background and Purpose—Although overweight is an important risk factor for cardiovascular disease in Western countries, the impact of overweight has not been well elucidated in Japan, where its prevalence is low.

Methods—A total of 104 928 Japanese (43 889 men and 61 039 women) aged 40 to 79 years, free of stroke, coronary heart disease, and cancer at entry participated in the Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study) between 1988 and 1990. Systematic surveillance was completed until the end of 1999, with 1 042 835 person years of follow-up, and the underlying causes of death were determined based on the International Classification of Diseases.

Results—There were 765 total strokes (191 intraparenchymal hemorrhages), 379 coronary heart diseases, and 1707 total cardiovascular diseases for men; and for women, there were 685 (145), 256, and 1432, respectively. Compared with persons with body mass index (BMI) 23.0 to 24.9, those with BMI ≥27.0 kg/m^2 had a higher risk of coronary heart disease; for men and women, the respective multivariate relative risk (95% CI) was 2.05 (1.35 to 3.13) and 1.58 (0.95 to 2.62). Persons with BMI <18.5 kg/m^2 had higher risk of total stroke and intraparenchymal hemorrhage, for men and women, the respective multivariate relative risk was 1.29 (1.01 to 1.49) and 1.92 (1.49 to 2.47) for total stroke and 1.96 (1.16 to 3.31) and 2.32 (1.36 to 3.97) for intraparenchymal hemorrhage. These excess risks did not alter materially when deaths within 5 years were excluded or when smoking status was taken into account.

Conclusions—For Japanese men and women, high BMI was associated with increased risk of coronary heart disease, whereas low BMI was associated with intraparenchymal hemorrhage. (*Stroke*. 2005;36:1377-1382.)

Key Words: body mass index ■ coronary heart disease ■ follow-up studies ■ mortality ■ stroke

Obesity is an important risk factor for cardiovascular disease in Western countries.[1–3] Persons with body mass index (BMI) ≥30 kg/m^2 had 1.5- to 3-fold higher mortality from cardiovascular disease.[3–7] More than 80% of the estimated deaths attributable to obesity occurred among individuals with BMI ≥30 kg/m^2.[1] In the United States, the prevalence of BMI ≥30 kg/m^2 increased from 12% in 1991 to 18% among adults ≥18 years of age in 1998.[2] But in Japan, the percentage of those with BMI ≥30 kg/m^2 was only 3.2% in 1998 among adults ≥15 years of age.[8] Low BMI was also associated with increased mortality from total deaths[3,5,6,9] and stroke.[10–12] However, a previous study showed that the inverse association for hemorrhagic stroke was confined to smokers.[4]

We examined comprehensively the relationships between BMI and mortality attributable to total stroke, stroke subtypes, coronary heart disease, and total cardiovascular disease among Japanese men and women in a large prospective cohort study.

Subjects and Methods

Japan Collaborative Cohort Study for Evaluation of Cancer Risk Sponsored by Monbusho (JACC Study) began in 1988 to 1990, when 110 792 individuals (46 465 men and 64 327 women) aged 40 to 79 years living in 45 communities across Japan participated in munic-

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ipal health screening examinations and completed self-administered questionnaires about current height and weight, their lifestyles, and medical histories of previous cardiovascular disease and cancer.[13] Informed consent was obtained from them when they completed the questionnaire. Follow-up surveys were conducted annually to verify the vital status of the participants. Among them, height and weight data were available for 45 893 men and 63 691 women. BMI was calculated in the formula of weight (kg)/height (m^2). Then we excluded 2576 men and 3288 women who had a history of stroke, coronary heart disease, or cancer at baseline. Therefore, 43 889 men and 61 039 women were enrolled in the present study.

For mortality surveillance in each community, investigators conducted systematic review for death certificates, all of which were forwarded to the public health center in the area of residency. Mortality data were sent centrally to the Ministry of Health and Welfare, and the underlying causes of death were coded according to the *International Classification of Diseases*, 9th Revision, from 1988 to 1994, and the 10th revision from 1995 to 1999 for the National Vital Statistics. Therefore, all deaths that occurred in the cohort were ascertained by death certificates from a public health center, except for subjects who died after they had moved from their original community, in which case subjects was treated as censored cases. The follow-up was conducted until the end of 1999, and the average follow-up for the participants was 9.9 years. The ethics committee of the University of Tsukuba approved the present study.

Statistical analyses were based on sex-specific incidence rates of stroke during the follow-up from between 1988 and 1990 to 1999. For each participant, periods of follow-up were calculated from the date of filling out the baseline questionnaire to his/her death, moving out of the community, or the end of 1999, whichever occurred first. The sex-specific relative risk of mortality from cardiovascular disease was defined as the death rate among participants in 6 categories of BMI (<18.5, 18.5 to 20.9, 21.0 to 22.9, 23.0 to 24.9, 25.0 to 26.9, and ≥27.0 kg/m^2). Because of the relatively low percentage of the categories of persons with BMI ≥30.0 kg/m^2, the categories of BMI 27.0 to 29.9 and ≥30.0 kg/m^2 were combined. We used categories of BMI 23.0 to 24.9 kg/m^2 as the reference because of the lowest age-adjusted mortality in both sexes.

Sex-specific age-adjusted means and proportions of selected cardiovascular risk factors and psychological factors were presented among the categories of BMI using analysis of covariance or χ^2 tests. Test for a linear trend across the BMI categories was conducted by linear regression or logistic regression model, adjusting for age using a median variable of BMI in each BMI category. The age-adjusted and multivariate-adjusted relative risks and their 95% CIs were calculated after adjustment for age and potential confounding factors by using the Cox proportional hazards model.

The confounding variables included smoking status (never-smoker; ex-smoker; and current smoker, 1 to 19, and ≥20 cigarettes per day), alcohol intake category (never-drinker; ex-drinker; and current drinker, ethanol 1 to 22, 23 to 45, 46 to 68, and ≥69 g per day), hours of walking (seldom, <30, 30 to 59, and ≥60 minutes per day), hours of sleep (<6.0, 6.0 to 6.9, 7.0 to 7.9, 8.0 to 8.9, and ≥9.0 hours per day), college or higher education (primary school, junior high school, high school, college or more), high perceived mental stress (low, medium, high), frequency of fish intake (never, 1, 1 to 2, 3 to 4, and ≥5 servings per week), hypertension (no, yes), and history of diabetes (no, yes). Hypertension was defined as ≥140 mm Hg of reported systolic blood pressure, ≥90 mm Hg of reported diastolic blood pressure, or antihypertensive medication use. The analysis was repeated by exclusion of death within 5 years of the follow-up and stratified by smoking status (never-smokers versus ex-smokers and current smokers). The significance of the interaction of smoking status with BMI was tested using an interaction term of continuous 2 variables in multivariate models.

Cause-specific mortality was determined by total cardiovascular disease (*International Classification of Disease*, 9th Revision codes 390 to 459, 10th revision, codes I01 to I99), total coronary heart disease (codes 410 to 414 and I20 to I25), and total stroke (430 to 438 and I60 to I69), separately. Further groupings of total strokes were also conducted as intraparenchymal hemorrhage (431 and I61), subarachnoid hemorrhage (430 and I60), and ischemic stroke (433 to 434 and I63).

Results

During the 9.9-year follow-up of 43 889 men and 61 039 women aged 40 to 79 years, 1 707 men and 1 432 women died from total cardiovascular disease. These deaths among men included 765 total strokes (191 intraparenchymal hemorrhages and 300 ischemic strokes) and 397 coronary heart diseases. The respective number of deaths among women was 685 (145 and 240) and 256. The percent distributions of BMI was 10.4% for <18.5, 22.2% for 18.5 to 20.9, 27.1% for 21.0 to 22.9, 22.9% for 23.0 to 24.9, 11.4% for 25.0 to 26.9, and 6.0% for ≥27.0 kg/m^2 among men. And percent distributions for women were 12.2%, 19.7%, 25.2%, 21.7%, 12.4%, and 8.8%, respectively. The mean BMI was 22.6 in men and 22.9 in women.

Table 1 shows sex-specific selected cardiovascular risk factors by 6 categories of BMI. For men and women, persons with BMI ≥27.0 kg/m^2 were more hypertensive, more diabetic, drunk more, and walked less compared with those with lower BMI categories. Men with BMI ≥27.0 kg/m^2 were younger, smoked less, and had higher fish intake, whereas women with BMI ≥27.0 kg/m^2 were less educated compared with those lower BMI categories. Men with BMI <18.5 kg/m^2 were less educated and more stressed compared with those higher BMI categories. We had the baseline data of serum total cholesterol for 27.6% of the total subjects. Serum total cholesterols levels were positively correlated with BMI for men and women. The proportion of serum total cholesterol <4.14 mmol/L (160 mg/dL) were 27.1% for BMI of <18.5 kg/m^2, declining to 11.5% for BMI of ≥27.0 kg/m^2 in men and 12.1% to 6.7% in women (data not shown).

Table 2 shows sex-specific age- and multivariate-adjusted relative risks of mortality from cardiovascular disease according to BMI categories. There was a U-shaped relationship between BMI and risk of mortality from total cardiovascular disease, with a nadir at BMI of 23.0 to 24.9 kg/m^2 for men and at BMI of 25.0 to 26.9 kg/m^2 for women (Figure). Persons with BMI ≥27.0 kg/m^2 had increased risk of mortality from coronary heart disease for men and women, although the trend did not reach statistical significance for women; the multivariate relative risk (95% CI) was 2.05 (1.35 to 3.13) for men and 1.58 (0.95 to 2.62) for women. When early deaths within 5 years were excluded, these relative risks were 1.94 (1.18 to 3.19) and 1.53 (0.88 to 2.67), respectively.

Persons with BMI <18.5 kg/m^2 had increased risk of mortality from total stroke, intraparenchymal hemorrhage, and total cardiovascular disease for both sexes; the respective multivariate relative risks were 1.29 (1.01 to 1.49), 1.96 (1.16 to 3.31), and 1.46 (1.24 to 1.72) for men and 1.92 (1.49 to 2.47), 2.32 (1.36 to 3.97), and 1.72 (1.45 to 2.04) for women. When early deaths were excluded, these relative risks were 1.15 (0.85 to 1.57), 2.35 (1.18 to 4.70), and 1.15 (0.93 to 1.42) for men and 1.74 (1.28 to 2.35), 2.25 (1.11 to 4.56), and 1.57 (1.28 to 1.94) for women. Women with BMI <18.5 kg/m^2 also had increased risk of mortality from coronary heart disease and ischemic stroke; the respective multivariate

TABLE 1. Sex-Specific Age-Adjusted Mean Values and Prevalence of Cardiovascular Risk Factors According to BMI

	BMI, kg/m²						
	<18.5	18.5–20.9	21–22.9	23–24.9	25–26.9	≥27.0	*P* for Trend
Men							
No. at risk	4561	9755	11 894	10 040	5014	2625	
Age, years	61.9	58.2	56.8	55.6	55.0	54.6	<0.001
Smoker, %	60.0	61.0	54.9	48.7	46.1	44.0	<0.001
Hypertension, %	42.4	39.5	45.4	52.4	58.2	65.4	<0.001
History of diabetes, %	5.8	6.1	6.4	6.7	8.0	8.8	<0.001
Ethanol intake, g/day	34.3	34.3	34.2	34.0	34.4	35.4	0.02
Walk ≥30 min/day, %	69.1	71.8	70.7	68.1	65.8	62.2	<0.001
Hours of sleep per day	7.6	7.5	7.5	7.4	7.4	7.4	<0.001
College or higher education, %	8.2	12.1	13.1	13.8	14.2	11.9	<0.001
High perceived mental stress, %	26.1	23.4	21.5	22.6	22.1	23.9	0.08
Frequency of fish intake, servings per week	6.7	6.9	7.1	7.1	7.0	7.2	0.02
Women							
No. at risk	7469	12023	15 376	13 232	7551	5388	
Age, years	62.0	56.5	56.1	56.3	57.0	57.0	<0.001
Smoker, %	7.8	5.6	4.5	4.5	4.5	7.0	<0.001
Hypertension, %	36.8	32.3	38.6	44.6	51.8	62.0	<0.001
History of diabetes, %	3.3	3.2	4.0	4.0	4.2	6.1	<0.001
Ethanol intake, g/day	11.6	10.2	9.9	10.6	9.8	13.0	0.001
Walk ≥30 min/day, %	70.6	73.9	73.2	71.0	70.5	69.2	<0.001
Hours of sleep per day	7.1	7.1	7.1	7.1	7.1	7.2	0.29
College or higher education, %	6.6	8.5	8.3	6.9	6.6	5.2	<0.001
High perceived mental stress, %	21.4	21.4	19.8	19.3	18.9	19.3	<0.001
Frequency of fish intake, servings per week	6.9	6.9	7.1	7.3	7.2	7.2	0.74

Means and proportion of selected risk factors using analysis of covariance or chi-square tests.

Test for a linear trend across of covariance the BMI categories was conducted by linear regression or logistic regression model, adjusting for age using a median variable of BMI in each BMI category.

relative risks were 1.76 (1.16 to 2.68) and 1.90 (1.22 to 2.96). When early deaths were excluded, these excess risks of mortality were reduced and were no longer statistically significant for coronary heart disease but remained significant for ischemic stroke; the respective multivariate relative risks were 1.42 (0.89 to 2.26) and 1.75 (1.08 to 2.85).

The associations between BMI and mortality were examined when stratified by smoking status (data not shown). The excess risk of mortality from coronary heart disease for BMI ≥27.0 kg/m² did not alter significantly according to smoking status. The multivariate relative risks for men were 1.47 (0.44 to 4.90) among never-smokers and 2.42 (1.50 to 3.91) among former and current smokers; the interaction was not statistically significant (P=0.16). The respective multivariate relative risks for women were 1.61 (0.87 to 2.98) and 1.11 (0.24 to 5.14; P for interaction=0.57). Similarly, the excess risks of intraparenchymal hemorrhage for BMI <18.5 kg/m² did not vary according to smoking status. The multivariate relative risks for men were 1.89 (0.51 to 6.97) among never-smokers and 1.95 (1.07 to 3.55) among former and current smokers; the interaction was not statistically significant (P=0.66). The respective multivariate relative risks for women were 2.04 (1.09 to 3.83) and 8.10 (0.63 to 105; P for interaction=0.96). These results did not alter materially when we categorized the smoking status into current smokers and noncurrent smokers.

Discussion

In the present large prospective study of middle-aged Japanese men and women, we observed that persons with BMI ≥27.0 kg/m² had 1.6- to 2.1-fold excess mortality from coronary heart disease, whereas those with BMI <18.5 kg/m² had 2.0- to 2.3-fold excess mortality from intraparenchymal hemorrhage and 1.3- to 2.0-fold excess mortality from total stroke. There was a U-shaped relationship between BMI and risk of mortality from total cardiovascular disease, which was consistent with the findings from previous studies in the United States.[2] These associations did not alter materially when we excluded deaths within 5 years of follow-up or smokers.

The excess risk of mortality from coronary heart disease among persons with BMI ≥27.0 kg/m² was consistent with the finding from a previous Japanese study.[14] A prospective cohort study[6] of >1 million US adults showed that persons with BMI ≥30.0 kg/m² had 1.5- to 3-fold higher mortality from total cardiovascular disease compared with those with BMI of 23.5 to 24.9 kg/m² and >80% of the estimated

TABLE 2. Relative Risks (RR) and 95% CIs of Mortality From Cardiovascular Disease According to BMI

	BMI, kg/m²					
	<18.5	18.5–20.9	21–22.9	23–24.9	25–26.9	≥27.0
Men						
Person y	41 672	94 620	117 610	99 932	50 054	26 198
Coronary heart disease						
No.	61	100	80	65	40	33
Age-adjusted RR	1.32 (0.92–1.88)	1.26 (0.92–1.73)	0.93 (0.67–1.30)	1.00	1.30 (0.88–1.93)	2.14 (1.41–3.25)
Multivariate RR	1.12 (0.77–1.62)	1.26 (0.92–1.72)	0.93 (0.67–1.30)	1.00	1.25 (0.84–1.86)	2.05 (1.35–3.13)
Total stroke						
No.	148	200	176	137	77	27
Age-adjusted RR	1.46 (1.15–1.84)	1.17 (0.94–1.46)	0.96 (0.77–1.21)	1.00	1.20 (0.90–1.58)	0.84 (0.56–1.27)
Multivariate RR	1.29 (1.01–1.49)	1.20 (0.96–1.49)	0.97 (0.78–1.22)	1.00	1.15 (0.87–1.52)	0.78 (0.52–1.18)
Intraparenchymal hemorrhage						
No.	38	42	53	27	22	9
Age-adjusted RR	2.26 (1.37–3.73)	1.37 (0.84–2.22)	1.54 (0.97–2.44)	1.00	1.70 (0.97–2.98)	1.37 (0.64–2.91)
Multivariate RR	1.96 (1.16–3.31)	1.42 (0.87–2.32)	1.57 (0.99–2.50)	1.00	1.62 (0.92–2.85)	1.25 (0.59–2.66)
Subarachnoid hemorrhage						
No.	13	23	18	17	6	3
Age-adjusted RR	1.52 (0.73–3.16)	1.32 (0.71–2.49)	0.87 (0.45–1.69)	1.00	0.72 (0.28–1.82)	0.70 (0.20–2.37)
Multivariate RR	1.67 (0.78–3.56)	1.32 (0.70–2.49)	0.86 (0.44–1.67)	1.00	0.70 (0.28–1.78)	0.64 (0.19–2.18)
Ischemic stroke						
No.	53	83	62	59	28	15
Age-adjusted RR	1.09 (0.75–1.59)	1.06 (0.76–1.49)	0.77 (0.54–1.10)	1.00	1.02 (0.65–1.60)	1.12 (0.63–1.97)
Multivariate RR	0.99 (0.67–1.46)	1.12 (0.80–1.56)	0.78 (0.55–1.12)	1.00	0.99 (0.63–1.56)	1.05 (0.60–1.86)
Total cardiovascular disease						
No.	345	425	397	288	166	86
Age-adjusted RR	1.63 (1.39–1.91)	1.19 (1.02–1.38)	1.04 (0.89–1.21)	1.00	1.23 (1.01–1.48)	1.27 (1.00–1.62)
Multivariate RR	1.46 (1.24–1.72)	1.21 (1.04–1.40)	1.05 (0.90–1.22)	1.00	1.17 (0.97–1.42)	1.19 (0.93–1.51)
Women						
Person y	72 145	120 653	155 651	133 965	76 145	54 186
Coronary heart disease						
No.	75	47	49	36	23	26
Age-adjusted RR	1.76 (1.18–2.64)	1.16 (0.75–1.80)	1.10 (0.71–1.69)	1.00	1.11 (0.67–1.87)	1.75 (1.05–2.89)
Multivariate RR	1.76 (1.16–2.68)	1.28 (0.83–1.98)	1.16 (0.75–1.79)	1.00	1.07 (0.63–1.80)	1.58 (0.95–2.62)
Total stroke						
No.	220	128	122	97	68	50
Age-adjusted RR	2.05 (1.60–2.62)	1.22 (0.93–1.59)	1.03 (0.79–1.34)	1.00	1.20 (0.88–1.64)	1.23 (0.88–1.73)
Multivariate RR	1.92 (1.49–2.47)	1.33 (1.02–1.73)	1.08 (0.83–1.41)	1.00	1.14 (0.84–1.56)	1.07 (0.76–1.50)
Intraparenchymal hemorrhage						
No.	50	21	28	22	13	11
Age-adjusted RR	2.44 (1.46–4.08)	0.95 (0.52–1.72)	1.06 (0.61–1.86)	1.00	1.01 (0.51–2.00)	1.19 (0.58–2.45)
Multivariate RR	2.32 (1.36–3.97)	1.04 (0.57–1.91)	1.11 (0.64–1.95)	1.00	0.95 (0.48–1.89)	1.02 (0.49–2.10)
Subarachnoid hemorrhage						
No.	31	28	25	28	17	14
Age-adjusted RR	1.39 (0.82–2.34)	1.04 (0.61–1.75)	0.76 (0.44–1.29)	1.00	1.03 (0.56–1.88)	1.19 (0.63–2.26)
Multivariate RR	1.53 (0.89–2.64)	1.15 (0.68–1.94)	0.79 (0.46–1.36)	1.00	0.96 (0.52–1.75)	1.03 (0.54–1.96)
Ischemic stroke						
No.	87	44	44	29	21	15
Age-adjusted RR	2.29 (1.49–3.50)	1.29 (0.81–2.07)	1.20 (0.75–1.92)	1.00	1.26 (0.72–2.21)	1.26 (0.67–2.34)
Multivariate RR	1.90 (1.22–2.96)	1.38 (0.86–2.22)	1.28 (0.80–2.04)	1.00	1.19 (0.68–2.08)	1.05 (0.56–1.97)
Total cardiovascular disease						
No.	448	257	264	216	125	122
Age-adjusted RR	1.79 (1.52–2.12)	1.08 (0.90–1.29)	0.99 (0.83–1.19)	1.00	1.00 (0.80–1.24)	1.35 (1.08–1.70)
Multivariate RR	1.72 (1.45–2.04)	1.16 (0.97–1.39)	1.03 (0.86–1.24)	1.00	0.95 (0.76–1.19)	1.18 (0.95–1.48)

Multivariate adjustment by age, hypertension, history of diabetes, current smoking, ethanol intake, hours of walking, hours of sleep, college or higher education, perceived mental stress, and frequency of fish intake.